27 February 2017
EMA/COMP/816520/2016
Procedure Management and Committees Support Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 06-08 December 2016

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

06 December 2016, 09:00-19:00, room 2F

07 December 2016, 08:30-20:00, room 2F

08 December 2016, 08:30-12:30, room 2F

Disclaimers

Some of the information contained in this set of minutes is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scopes listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also vary during the course of the review. Additional details on some of these procedures will be published in the COMP meeting reports once the procedures are finalised.

Of note, this set of minutes is a working document primarily designed for COMP members and the work the Committee undertakes.

Further information with relevant explanatory notes can be found at the end of this document.

Note on access to documents

Some documents mentioned in the minutes cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

An agency of the European Union

© European Medicines Agency, 2017. Reproduction is authorised provided the source is acknowledged.

Table of contents

1. Introduction

1.1. Welcome and declarations of interest of members and experts

In accordance with the Agency's policy on handling of declarations of interests of scientific committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced that no restriction in the involvement of meeting participants in upcoming discussions was identified as included in the pre-meeting list of participants and restrictions.

Participants in this meeting were asked to declare any changes, omissions or errors to their declared interests and/or additional restrictions concerning the matters for discussion. No new or additional interests or restrictions were declared.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure and as included in the list of participants. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 23 or more members were present in the room). All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

1.2. Adoption of agenda

The agenda for 06-08 December 2016 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 03-04 November 2016 were adopted with no amendments and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. - EMA/OD/200/16

Treatment of paediatric stroke

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

Paediatric stroke should be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

The sponsor used several arguments to support the use of the product in neonatal and childhood stroke rather than the adult stroke. No pharmacological arguments for the use of the product only in paediatric population were given.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of paediatric stroke, the sponsor should further elaborate on:

- the overlapping nature of the condition as applied for and to discuss whether this can be considered a valid subset of other orphan conditions
- the preclinical data in which the product was used to treat both juvenile and adult hypoxic-ischaemic brain injury or any other data which would help define the specificity of the product to the proposed indication;
- the positioning of the product in the standard of care. The sponsor is invited to elaborate on the way the product would fit within the diagnosis/treatment algorithm for both neonatal and childhood strokes.

In the written response, and during an oral explanation before the Committee on 06 December 2016, the sponsor provided additional literature sources and discussed the fact that the plasticity of the younger brain is greater than an adult brain and therefore the product is expected to have a much higher efficacy in paediatric population. The committee questioned this argument for delineating the condition from adult stroke based on the fact that, albeit less active, the product would nonetheless have some pharmacodynamic activity in adult brain as well. The provision of subset specificity of the product was therefore not met. In addition, the overlap of paediatric stroke and other orphan conditions was discussed. In summary it was considered that paediatric stroke was not acceptable as an orphan condition for orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation on 07 December 2016, prior to final opinion.

2.1.2. [5,10,15,20-Tetrakis(4-carboxyphenyl)-21H,23H-porphine] manganese(III) chloride - EMA/OD/205/16

Institut Pasteur; Treatment of Cockayne syndrome

COMP coordinator: Ingeborg Barisic

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

Xeroderma pigmentosum-Cockayne syndrome (XP-CS) should be justified as a part of the proposed condition. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of Cockayne syndrome, the sponsor should further elaborate on:

- how the results obtained in vitro can predict clinically meaningful outcome in patients affected by the condition;
- the availability of preclinical in vivo or in vitro models in which clinically meaningful outcomes could be measured, e.g transgenic models with mild phenotype or CS induced pluripotent stem cells.

In the written response, and during an oral explanation before the Committee on 06 December 2016, the sponsor discussed the condition and clarified that patients with Xeroderma pigmentosum-Cockayne syndrome are part of the same spectrum as Cockayne syndrome patients however, carry mutations in different genes and present distinct clinical features, especially with respect to neurological and dermatological symptoms. In light of the distinct pathophysiological mechanisms, the sponsor agreed with the COMP to exclude Xeroderma pigmentosum-Cockayne syndrome from the orphan condition.

Regarding the medical plausibility, the sponsor described the various available preclinical models including transgenic models and induced pluripotent stem cell models from patient cells. The sponsor also critically discussed the available preclinical in vitro findings demonstrating that treatment with the proposed product was able to restore mitochondrial respiration, which has been shown to be altered in Cockayne syndrome patients. The COMP considered that the generated evidence was sufficient to establish the assumption of medical plausibility for the purpose of orphan designation.

The Committee agreed that the condition, Cockayne syndrome, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing [5,10,15,20-tetrakis(4-carboxyphenyl)-21H,23H-porphine]manganese(III) chloride was considered justified based on preclinical data demonstrating that treatment was able to restore mitochondrial respiration that is altered in patients affected by the condition.

The condition is life-threatening with an average lifespan of 12 years and chronically debilitating due to growth and developmental abnormalities with severe disabilities and photosensitivity.

The condition was estimated to be affecting less than 0.01 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for [5,10,15,20-tetrakis(4-carboxyphenyl)-21H,23H-porphine]manganese(III) chloride, for treatment of Cockayne syndrome, was adopted by consensus.

2.1.3. - EMA/OD/203/16

Treatment of Rett syndrome

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

The sponsor presented published literature data to support activity of the product in several preclinical models that were not specific for the proposed condition. No data with the use of the product in models of the condition or in patients were presented.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of Rett syndrome, the sponsor should further elaborate on:

- any data in the model of Rett syndrome
- the relevance of the preclinical models used for the treatment of Rett syndrome, and the interpretation of the results obtained in the experiments.

In the written response, and during an oral explanation before the Committee on 06 December 2016, the sponsor presented more detailed data on the similarities of the presented preclinical models and Rett syndrome models. No data with the use of specific Rett models or patients were presented. In the absence of such data the medical plausibility could not be established.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 06 December 2016, prior to final opinion.

2.1.4. - EMA/OD/210/16

Prevention of necrotising enterocolitis

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for the prevention of necrotising enterocolitis, the sponsor should further elaborate on the extrapolation of the results from published studies to the intended clinical use of the proposed product in necrotising enterocolitis.

In addition the sponsor is invited to further elaborate on potential safety issues related to the proposed product.

In the written response, and during an oral explanation before the Committee on 06 December 2016, the sponsor discussed the overlap between the proposed product and the published studies on similar products that were presented to support the medical plausibility. The COMP acknowledged certain similarities but was still of the opinion that data with the proposed product would be needed in order to establish the medical plausibility.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 06 December 2016, prior to final opinion.

2.1.5. 5-aminolevulinic acid - EMA/OD/215/16

Centre Hospitalier Universitaire de Lille; Treatment of glioma

COMP coordinator: Ingrid Wang

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Significant benefit

Satisfactory methods of treatment of the condition have been authorised in the European Union. It is unclear what is the intended positioning of the 5-ALA-PDT treatment and this needs further contextualisation. Thus, the sponsor is requested to further discuss the arguments provided for significant benefit. In particular the sponsor is should elaborate on:

  - how will the treatment be used during development, i.e. interstitial or intraoperative treatment;
  - what is the intended line of treatment (primary treatment or for recurrent disease, operable or inoperable disease);
  - the significant benefit over authorised products/standard of care should be argued taking into account the context of the intended treatment.

In the written response, the sponsor discussed the product extensively vs. authorised carmustine wafers and highlighted the added efficacy of the product when used in combination with temozolomide. The committee considered these explanations satisfactory and came to a positive opinion and cancelled the oral hearing.

The Committee agreed that the condition, glioma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 5-aminolevulinic acid was considered justified based on clinical data from patients demonstrating improved survival.

The condition is chronically debilitating due to symptoms caused by compression by the tumour on the surrounding brain tissue including headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality and cognitive impairment. The condition is life-threatening, with poor 5-year survival of less than 5% for glioblastoma multiforme patients.

The condition was estimated to be affecting approximately 2.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 5-aminolevulinic acid will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate that the product synergises with the authorised product. Early clinical data shows an improved survival when the product is used in combination with the standard of care. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 5-aminolevulinic acid, for treatment of glioma, was adopted by consensus.

2.1.6. - EMA/OD/214/16

Treatment of status epilepticus

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

Status epilepticus (SE) should be justified as a distinct medical entity or a valid subset. In particular the sponsor is invited to justify why status epilepticus would be considered a distinct medical entity rather than a stage or a form of epilepsy. This is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

In addition the sponsor is invited to further elaborate on the relevance of the preclinical studies presented, to the intended clinical use of the product.

- Number of people affected

The sponsor discussed some publications and one expert opinion reporting that the annual incidence of SE would be less than 5 in 10,000 in the EU.

However it is not clear how this incidence was calculated, e.g. in relation to whether multiple episodes in the same patients have been considered to contribute to the final estimate. Indeed the annual incidence of Generalized Tonic-Clonic Seizures (which represents only a part of the cases of SE) has been estimated to be approximately 18-28/100,000 persons, and up to 61/100,000 (Trinka et al, 2015; Shorvon 1994), even when a time limit of 30 minutes for the definition of SE was considered.

The recent ILAE proposal of SE classification (Trinka et al, 2015) includes many SE types (e.g. CSWS or ESES, hypsarrhythmia, myoclonic status) not included in previous classifications, which do not seem to have been discussed by the sponsor, and the most recent definition of SE is based on duration of seizures of > of 5' (GTCS) or 10' (focal with impaired consciousness), which may also have an impact.

Therefore the sponsor is invited to further justify the statement that the incidence of SE would be less than 5 in 10,000.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition. The sponsor should therefore elaborate further on the significant benefit of the proposed product based on its mechanism of action.

In the written response, and during an oral explanation before the Committee on 06 December 2016, the sponsor proposed that the definition of status epilepticus be based on the ILAE Definition as stated in Fisher 2014. The COMP was of the opinion that the proposed definition was superseded by a more recent definition of the proposed condition where the time of the seizure for diagnostic purposes was revised.

Regarding the acceptability of the condition for orphan designation, the COMP discussed whether status epilepticus could be perceived as a degree of severity of epilepsy. Although there is a definition for status epilepticus in the ILAE 2014 paper, this field is evolving and would affect the heterogeneity of the different aetiological causes of the condition as well as the period of time a seizure stated to be status epilepticus is acceptable.

Regarding prevalence, the COMP was of the opinion that the revision of the period of seizure for diagnosis of status epilepticus would include a broader population than that defined by the sponsor, which would affect the final prevalence calculation. An earlier definition of a 30-minute seizure proposed by the sponsor was considered surpassed by a more recent one which accepts the time of 5 minutes for Generalized Tonic-Clonic and 10-minutes for focal

as defining a seizure which can be classified as status epilepticus. This would ultimately affect the prevalence calculation as the proposed changes would increase the potential number of patients captured in the prevalence calculation. Regarding the epidemiological index, the sponsor has proposed that status epilepticus prevalence should be established as an incidence. The argument supporting this assumption was that the status epilepticus generally occurs only a limited number of times in a year and is of short duration. The COMP did not agree with this assumption and it was noted by the COMP coordinators that status epilepticus can in certain patients occurs several times over several years. The COMP was therefore of the opinion that the prevalence calculation was incomplete and that the prevalence may well be above the threshold of 5 in 10,000.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 08 December 2016, prior to final opinion.

2.1.7. - EMA/OD/199/16

Treatment of pancreatic cancer

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

The COMP has noted the absence of data with the specific product as proposed for designation in the specific setting as applied for. Without data to justify the criteria for designation the application cannot be evaluated.

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of pancreatic cancer, the sponsor should further elaborate on:

  - the available in vivo data with the specific product under review in the specific setting i.e. pancreatic cancer and not other malignancies. A detailed description of the experimental settings, treatments, evaluations and results is required in order to proceed with the evaluation of the orphan medicinal product application.
  - the open and uncontrolled nature of the preliminary clinical observations. The sponsor should provide the particulars of the treated patients' backgrounds and concomitant medications, in order to justify the claimed improvements in survival.

- Significant benefit

The arguments on significant benefit are based on a new mechanism of action but no data are presented supporting a clinically relevant advantage or major contribution to patient care. Notwithstanding that the mechanism of action remains unknown, without such data in either in vivo experimental settings or in preliminary clinical observations, the significant benefit may not be considered.

In the written response, and during an oral explanation before the Committee on 07 December 2016, the sponsor elaborated on the available in vivo data in pancreatic cancer models and further provided clinical narratives in four patients affected by the proposed condition.

The clinical cases were discussed in further detail and an improved survival was argued as compared to expectations. The COMP questioned the variability of the expected survival and the use of amylase as a concomitant treatment. The relevance of older studies for the current standard of care was also questioned. Due to the open and uncontrolled nature of the presented observations, the proposed arguments were not considered acceptable by the committee to support medical plausibility.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 08 December 2016, prior to final opinion.

2.1.8. - EMA/OD/196/16

Treatment of Guillain-Barré syndrome

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 20 November 2016, prior to responding to the list of issues.

2.1.9. Pioglitazone hydrochloride - EMA/OD/189/16

Regiomedica GmbH; Treatment of sudden sensorineural hearing loss

COMP coordinator: Armando Magrelli

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Proposed condition

The sponsor is invited to justify the exclusion of other types of sensorineural hearing loss from the proposed condition.

- Prevalence

The sponsor is invited to justify the epidemiological index used for the prevalence calculation in the context of the duration of the proposed condition.

The sponsor is requested to provide a sensitivity analysis of all assumptions used and update the estimate in n/10,000 format for the time the application is made.

- Significant benefit

The arguments on significant benefit are based on a new mechanism of action but no data are presented supporting a clinically relevant advantage or major contribution to patient care. A discussion based on data juxtaposing the product with the authorised counterparts is expected. Without such data in either in vivo experimental settings or in preliminary clinical observations, the significant benefit may not be considered.

In the written response, and during an oral explanation before the Committee on 06 December 2016, the sponsor argued that the acute form can be discerned from other forms of sensorineural hearing loss on the basis of acute mechanical injury to the hairy cells that ultimately results in their loss. The COMP took into consideration a recent opinion on that indication and accepted the indication, yet by improving its articulation to “sudden

sensorineural hearing loss" as described in the publication Stachler and colleagues (Otolaryngology–Head and Neck Surgery 2012:146(1S) S1–S35).

The response pertaining to the prevalence question asserted that the patients either recover or stabilise within a period of approximately 3 months. Moreover, the applicant claimed that it is not possible to provide a sensitivity analysis for each study directly, but that the majority of the independent ones come to very similar values (range 1.02 – 2.75/10,000) all of which fall below the orphan definition threshold. The COMP reflected on some of these uncertainties. The committee considered an estimate of prevalence of approximately 4 in 10,000 at the time of orphan drug designation.

Significant benefit was proposed on improved efficacy and increased availability through a central authorisation. In line with the new Commission notice (2016/C 424/03) for applicants by the European commission, the argument for increased availability was not accepted by the committee due to lack of evidence. New preclinical in vitro as well as preclinical in vivo data in valid preclinical models were presented in the responses to support the expected improved efficacy. The COMP considered that the data demonstrated that in contrast to authorised products the new proposed product targets an acute mechanical disorder for which the authorised treatments would not have an effect. The COMP considered that to be a clinically relevant advantage.

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of sudden sensorineural hearing loss.

The Committee agreed that the condition, sudden sensorineural hearing loss, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing pioglitazone hydrochloride was considered justified based on preclinical data in a model of the condition demonstrating improved hearing recovery.

The condition is chronically debilitating due to sudden and often irreversible loss of hearing in one or both ears as well as symptoms associated with hearing loss such as tinnitus, vertigo and confusion.

The condition was estimated to be affecting approximately 4 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing pioglitazone hydrochloride will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate that the product may have a disease modifying effect and improve hearing recovery. This compares favourably to the authorised products, which are used to alleviate the symptoms accompanying hearing loss or vascular disorders of the ear. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for pioglitazone hydrochloride, for treatment of sudden sensorineural hearing loss, was adopted by consensus.

2.1.10. - EMA/OD/192/16

Treatment of pulmonary arterial hypertension

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for the treatment of pulmonary arterial hypertension, the sponsor should further elaborate on the methodology of the preclinical studies, where treatment administration was started at the same time as the administration of monocrotaline, and the relevance of these studies to the intended therapeutic use of the proposed product.

In the written response, and during an oral explanation before the Committee on 07 December 2016, the sponsor discussed the clinical relevance of preclinical models where treatment was initiated at the same time as the monocrotaline (MCT) challenge, and other pulmonary arterial hypertension models (PAH). In relation to the timing of treatment in the MCT model, the sponsor argued that treatment administration within 24 hours from MCT challenge is defined as immediate treatment while from 1-28 days after MCT challenge it is defined as delayed treatment. The COMP acknowledged the explanation of the sponsor but considered that the methodology of the MCT model that was not sufficiently representative of a treatment setting.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 08 December 2016, prior to final opinion.

2.1.11. Leuprorelin acetate - EMA/OD/097/16

Stichting Centre for Human Drug Research (CHDR); Treatment of congenital hypogonadotropic hypogonadism

COMP coordinator: Vallo Tillmann

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

The COMP considered to change the proposed condition to congenital hypogonadotropic hypogonadism in line with the Expert consensus document: European Consensus Statement on congenital hypogonadotropic hypogonadism--pathogenesis, diagnosis and treatment (Nat Rev Endocrinol. 2015 Sep;11(9):547-64).

The current preclinical data are not considered sufficient to establish medical plausibility. To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of congenital hypogonadotropic hypogonadism, the sponsor should present additional data in valid preclinical models that reflect the pathology of the condition, or preliminary clinical data from patients affected by the condition. Otherwise, medical plausibility cannot be established.

- Significant benefit

The sponsor is requested to supply a full list of all authorised products in the EU including all national authorisations. The sponsor is invited to clarify, if there is any data with the proposed product that could support the presented arguments for significant benefit on a clinically relevant advantage.

In the written response, the sponsor agreed with the COMP and changed the orphan condition to congenital hypogonadotropic hypogonadism in line with a recent expert consensus document (Nat Rev Endocrinol. 2015 Sep;11(9):547-64).

Furthermore, the sponsor provided additional evidence to support medical plausibility and significant benefit. This evidence stems from published scientific literature indicating that gonadotropin-releasing hormone analogue therapy is able to improve semen parameters, serum gonadotropin and testosterone levels. In addition the COMP acknowledged that gonadotropin-releasing hormone analogue therapy is currently recommended by a recent clinical consensus treatment guideline. In totality, the COMP considered that there was sufficient evidence to support the assumption of medical plausibility for orphan designation. In line with the evidence for medical plausibility, the COMP considered that current authorised products are not able to achieve the same treatment effects on testosterone levels, gonadotropin levels and fertility. The COMP therefore considered that the assumption of significant benefit is sufficiently demonstrated for the purpose of orphan designation.

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of congenital hypogonadotropic hypogonadism.

The Committee agreed that the condition, congenital hypogonadotropic hypogonadism, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing leuprorelin acetate was considered justified based on preclinical data demonstrating that treatment with the product can increase testosterone levels, which is supported by clinical data from literature and treatment recommendations.

The condition is chronically debilitating due to somatic dysmorphism, eunuchoid appearance in males and infertility. If left untreated, the condition manifests in sexual dysfunction with reduction of libido and potency.

The condition was estimated to be affecting approximately 2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing leuprorelin acetate will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate that treatment with the product can increase testosterone levels. In addition, the product has the potential to improve gonadotropin levels and fertility. This is supported by published scientific literature and consensus treatment guidelines. Current authorised products are not able to achieve the same treatment effects. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for leuprorelin acetate, for treatment of congenital hypogonadotropic hypogonadism, was adopted by consensus.

2.1.12. Hydroxychloroquine - EMA/OD/213/16

Centre Hospitalier Universitaire d' Angers; Treatment of antiphospholipid syndrome

COMP coordinator: Geraldine O'Dea

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Number of people affected

The sponsor has provided prevalence calculations for the primary and secondary forms, which in sum are close or above the threshold 5 per 10,000. As a consequence, the sponsor has not adequately demonstrated that the condition is below the threshold.

- The sponsor should justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. Please provide primary epidemiological literature on the condition in peer reviewed journals, rather than quoting prevalence statements in review articles and other databases.

- The sponsor should describe and justify the methodology used for the prevalence calculation.

- It seems that the sponsor has excluded part of the population that is affected by the secondary forms with other underlying auto-immune diseases than systemic lupus erythematosus

- The sponsor should re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition, and given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor should perform a sensitivity analysis of the reported calculations.

For the calculation and presentation of the prevalence estimate it is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

In the written response, the sponsor provided a revised prevalence estimate of 0.22 to 1.8 per 10,000 by outlining valid epidemiological literature on the primary form and all types of secondary forms of antiphospholipid syndrome. The data sources consisted of published and peer-reviewed primary epidemiological literature, as well as national and European registry data from the Europhospholipid group. In totality, the COMP accepted the methodology and data sources. The condition was estimated to be affecting less than 2 in 10,000 persons in the European Union, at the time the application was made.

The Committee agreed that the condition, antiphospholipid syndrome, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing hydroxychloroquine was considered justified based on preliminary clinical data demonstrating that the product was able to prevent thrombotic recurrence in primary antiphospholipid syndrome patients.

The condition is life-threatening and chronically debilitating due to the high risk of thrombosis and obstetrical complications, and the occurrence of myocardial infarction and stroke.

The condition was estimated to be affecting less than 2 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for hydroxychloroquine, for treatment of antiphospholipid syndrome, was adopted by consensus.

2.1.13. - EMA/OD/212/16

Treatment of multiple myeloma

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of multiple myeloma, the sponsor should further elaborate on the preliminary clinical data in patients with multiple myeloma.

- Number of people affected

For the calculation and presentation of the prevalence estimate it is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor should justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor should describe and justify the methodology used for the prevalence calculation.

The sponsor should re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition, and given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor should perform a sensitivity analysis of the reported calculations.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition.

The sponsor has provided preliminary clinical data in patients showing stable disease. There have been many new products which have recently been authorised for use in this condition making the relevance of the data submitted difficult to establish.

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the preliminary clinical study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

In the written response, and during an oral explanation before the Committee on 07 December 2016, the sponsor presented a revised prevalence calculation, which established the prevalence at 3.32 in 10,000 in Europe. This was accepted by the COMP.

The COMP did not accept the assumption proposed by the sponsor regarding the clinically relevant advantage to support significant benefit. The sponsor presented additional data regarding the efficacy in patients. The sponsor made indirect comparisons of their product to other authorised products. The COMP was of the opinion that while the additional data was of interest, the assumptions made by the sponsor were not warranted by the preliminary nature of the data.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 08 December 2016, prior to final opinion.

2.2. For discussion / preparation for an opinion

2.2.1. (6aR, 10aR)-3-(1',1'-dimethylheptyl)-delta8-tetrahydro-cannabinol-9-carboxylic acid - EMA/OD/243/16

TMC Pharma Services Ltd; Treatment of systemic sclerosis

COMP coordinator: Dan Henrohn/Geraldine O'Dea

The Committee agreed that the condition, systemic sclerosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing (6aR, 10aR)-3-(1',1'-dimethylheptyl)-delta-8-tetrahydro-cannabinol-9-carboxylic acid was considered justified based on in vivo preclinical data demonstrating antifibrotic effects with the proposed product.

The condition is chronically debilitating and life-threatening due to the deposition of collagen in the skin and in internal organs such as kidneys, heart, lungs and gastrointestinal tract, leading to severe complications such as pulmonary hypertension, progressive dysphagia, sclerodermal renal crisis and cardiac failure.

The condition was estimated to be affecting approximately 3.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (6aR, 10aR)-3-(1',1'-dimethylheptyl)-delta-8-tetrahydro-cannabinol-9-carboxylic acid will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate an antifibrotic effect of the proposed product which is directly associated with the condition and not targeted by the currently authorised treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for (6aR, 10aR)-3-(1',1'-dimethylheptyl)-delta-8-tetrahydro-cannabinol-9-carboxylic acid, for treatment of systemic sclerosis, was adopted by consensus.

2.2.2. 3-pentylbenzeneacetic acid sodium salt - EMA/OD/231/16

ProMetic Pharma SMT Limited; Treatment of Alström syndrome

COMP coordinator: Vallo Tillmann

The Committee agreed that the condition, Alström syndrome, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 3-pentylbenzeneacetic acid sodium salt was considered justified based on preliminary clinical data in patients with the condition showing an improvement in liver fibrosis.

The condition is chronically debilitating due to permanent blindness, deafness, and Type 2 diabetes and life-threatening due to progressive multiple organ failure. The life expectancy is usually reduced and the patients rarely live beyond 50 years of age.

The condition was estimated to be affecting approximately 0.01 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for 3-pentylbenzeneacetic acid sodium salt, for treatment of Alström syndrome, was adopted by consensus.

2.2.3. - EMA/OD/229/16

Treatment of diffuse large B cell lymphoma

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the January 2017 meeting.

2.2.4. - EMA/OD/080/15

Treatment of fragile X syndrome

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the January 2017 meeting.

2.2.5. Antroquinonol - EMA/OD/241/16

Biological Consulting Europe Ltd; Treatment of pancreatic cancer

COMP coordinator: Brigitte Bloechl-Daum

The Committee agreed that the condition, pancreatic cancer, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing antroquinonol was considered justified based on preclinical data in valid models of the condition, showing reduction of tumour size with the proposed product.

The condition is chronically debilitating because of pain in the upper abdomen, loss of appetite, nausea, vomiting, weight loss, jaundice, fatigue, weakness and depression; and life-threatening with a median survival of about 6 months.

The condition was estimated to be affecting approximately 1.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing antroquinonol will be of significant benefit to those affected by the condition. This is based on preclinical data showing more pronounced reduction of tumour growth with the proposed product in combination with gemcitabine and paclitaxel as compared to only gemcitabine and paclitaxel, currently authorised for the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by pancreatic cancer.

A positive opinion for antroquinonol, for treatment of pancreatic cancer, was adopted by consensus.

2.2.6. Autologous dendritic cells ex vivo incubated with zebularine and factor VIII - EMA/OD/238/16

Idogen AB; Treatment of haemophilia A

COMP coordinator: Armando Magrelli

Following review of the application by the Committee, it was agreed to broaden/rename the active substance to autologous dendritic cells incubated ex vivo with zebularine and factor VIII.

The Committee agreed that the condition, haemophilia A, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing autologous dendritic cells incubated ex vivo with zebularine and factor VIII was considered justified based on pre-clinical in vivo data showing an improvement in the Factor VIII activity following treatment.

The condition is chronically debilitating due to recurrent bleeding in joints, gastrointestinal tract or in surgery, which may also be life-threatening.

The condition was estimated to be affecting approximately 1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous dendritic cells incubated ex vivo with zebularine and factor VIII will be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical in vivo data that demonstrate an improvement in Factor VIII activity following treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous dendritic cells incubated ex vivo with zebularine and factor VIII, for treatment of haemophilia A, was adopted by consensus.

2.2.7. - EMA/OD/211/16

Treatment of glioma

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the January 2017 meeting.

2.2.8. - EMA/OD/235/16

Treatment of perinatal intracranial haemorrhage

The sponsor formally withdrew the application for orphan designation on 07 December 2016, prior to responding to the list of issues.

2.2.9. - EMA/OD/216/16

Treatment of ovarian cancer

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the January 2017 meeting.

2.2.10. - EMA/OD/246/16

Treatment of non-infectious uveitis

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the January 2017 meeting.

2.2.11. - EMA/OD/244/16

Treatment of primary ciliary dyskinesia

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the January 2017 meeting.

2.2.12. - EMA/OD/232/16

Treatment of glycogen storage disease type II (Pompe's disease)

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the January 2017 meeting.

2.2.13. Doxorubicin hydrochloride (in a lipid-based pegylated nanoparticle modified with a 31-aminoacid peptide targeting nucleolin) - EMA/OD/250/16

TREAT U, S.A.; Treatment of malignant mesothelioma

COMP coordinator: Katerina Kopečková/Ingrid Wang

Following review of the application by the Committee, it was agreed to broaden/rename the active substance to doxorubicin hydrochloride in a lipid-based pegylated nanoparticle modified with a 31-aminoacid peptide targeting nucleolin.

The Committee agreed that the condition, malignant mesothelioma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing doxorubicin hydrochloride in a lipid-based pegylated nanoparticle modified with a 31-aminoacid peptide targeting nucleolin was considered justified based on inhibition of tumour growth in an in vivo model of the condition, as assessed by imaging.

The condition is life-threatening due to the invasion of the pleura leading to pleural effusions, dyspnoea and malignant ascites. Local invasion may also result in obstruction of the superior vena cava, cardiac tamponade, and spinal cord compression. Patients with pleural mesothelioma usually die due to increasing tumour bulk that gradually fills the hemithorax causing progressive respiratory compromise ("incarceration" of the lungs), pneumonia, or myocardial dysfunction with arrhythmias. In patients with peritoneal mesothelioma,

distension due to ascites, abdominal pain, and organ impairment such as bowel obstruction are observed.

The condition was estimated to be affecting less than 1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing doxorubicin hydrochloride in a lipid-based pegylated nanoparticle modified with a 31-aminoacid peptide targeting nucleolin will be of significant benefit to those affected by the condition. The sponsor has provided in vivo data that demonstrate that treatment with the product results in improved tumour growth inhibition in tumours resistant to existing therapies. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for doxorubicin hydrochloride in a lipid-based pegylated nanoparticle modified with a 31-aminoacid peptide targeting nucleolin, for treatment of malignant mesothelioma, was adopted by consensus.

2.2.14. - EMA/OD/233/16

Treatment of Lennox-Gastaut syndrome

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the January 2017 meeting.

2.2.15. - EMA/OD/239/16

Treatment of pancreatic cancer

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the January 2017 meeting.

2.2.16. Fluticasone propionate - EMA/OD/230/16

Adare Pharmaceuticals srl; Treatment of eosinophilic oesophagitis

COMP coordinator: Olimpia Neagu

The Committee agreed that the condition, eosinophilic oesophagitis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing fluticasone propionate was considered justified based on improvement in symptoms and histology in treated patients affected by the condition.

The condition is chronically debilitating due to chronic oesophageal inflammation with development of dysphagia that affects dietary intake, oesophageal stenosis and fragility of the oesophageal wall.

The condition was estimated to be affecting approximately 3.8 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for fluticasone propionate, for treatment of eosinophilic oesophagitis, was adopted by consensus.

2.2.17. Genetically modified adeno-associated viral vector serotype 9 expressing shRNA as well as a codon-optimised shRNA-insensitive wildtype PABPN1 - EMA/OD/194/16

Clinipace GmbH; Treatment of oculopharyngeal muscular dystrophy

COMP coordinator: Pauline Evers/Michel Hoffmann

Following review of the application by the Committee, it was agreed to broaden/rename the active substance to genetically modified adeno-associated viral vector serotype 9 expressing shRNA as well as a codon-optimised shRNA-insensitive wildtype PABPN1.

The Committee agreed that the condition, oculopharyngeal muscular dystrophy, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing genetically modified adeno-associated viral vector serotype 9 expressing shRNA as well as a codon-optimised shRNA-insensitive wildtype PABPN1 was considered justified based on pre-clinical in vivo data showing an improvement in muscle strength.

The condition is chronically debilitating due to lowering (ptosis) of the eyelids and swallowing difficulties (dysphagia). With disease progression, additional skeletal muscles can be affected including the proximal muscles of the lower limb affecting gait.

The condition was estimated to be affecting approximately 0.1 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for genetically modified adeno-associated viral vector serotype 9 expressing shRNA as well as a codon-optimised shRNA-insensitive wildtype PABPN1, for treatment of oculopharyngeal muscular dystrophy, was adopted by consensus.

2.2.18. - EMA/OD/251/16

Treatment of sickle cell disease

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the January 2017 meeting.

2.2.19. Human donor haematopoietic stem and progenitor cells that have been treated ex vivo with the protein transduction domain of the HIV-1 transactivation protein fused to MYC transcription factor - EMA/OD/191/16

Coté Orphan Consulting UK Limited; Treatment in haematopoietic stem cell transplantation

COMP coordinator: Frauke Naumann-Winter

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment in haematopoietic stem cell transplantation and to broaden/rename the active substance to human donor haematopoietic stem and progenitor cells that have

been treated ex vivo with the protein transduction domain of the HIV-1 transactivation protein fused to MYC transcription factor.

The Committee agreed that the condition, haematopoietic stem cell transplantation, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing human donor haematopoietic stem and progenitor cells that have been treated ex vivo with the protein transduction domain of the HIV-1 transactivation protein fused to MYC transcription factor was considered justified based on improved engraftment in pre-clinical in vivo models of the condition.

The condition is life-threatening and chronically debilitating due to susceptibility to severe infections and complications such as graft-versus-host disease.

The condition was estimated to be affecting approximately 0.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing human donor haematopoietic stem and progenitor cells that have been treated ex vivo with the protein transduction domain of the HIV-1 transactivation protein fused to MYC transcription factor will be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical in vivo data that supports potential improved engraftment in a larger patient population than currently approved products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for human donor haematopoietic stem and progenitor cells that have been treated ex vivo with the protein transduction domain of the HIV-1 transactivation protein fused to MYC transcription factor, for treatment in haematopoietic stem cell transplantation, was adopted by consensus.

2.2.20. Human hepatoma cell line HepaRG in bioartificial liver - EMA/OD/222/16

Hep-Art Medical Devices BV; Treatment of acute liver failure

COMP coordinator: Daniel O'Connor

The Committee agreed that the condition, acute liver failure, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing human hepatoma cell line HepaRG in bioartificial liver was considered justified based on pre-clinical in vivo and preliminary clinical data showing better survival.

The condition is life threatening in particular due to the development of encephalopathy with intracranial hypertension, multi-organ failure and sepsis.

The condition was estimated to be affecting approximately 0.06 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing human hepatoma cell line HepaRG in

bioartificial liver will be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical and clinical data that demonstrate improved survival providing a bridging option for liver transplantation. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for human hepatoma cell line HepaRG in bioartificial liver, for treatment of acute liver failure, was adopted by consensus.

2.2.21. Humanised, immunoglobulin G isotype 1 monoclonal antibody directed specifically against the receptor-binding site of human placental growth factor - EMA/OD/240/16

Oncurious NV; Treatment of medulloblastoma

COMP coordinator: Bożenna Dembowska-Bagińska

Following review of the application by the Committee, it was agreed to broaden/rename the active substance to humanised IgG1 monoclonal antibody against the receptor-binding site of human placental growth factor.

The Committee agreed that the condition, medulloblastoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing humanised IgG1 monoclonal antibody against the receptor-binding site of human placental growth factor was considered justified based on preclinical data showing improved survival in valid models of the condition.

The condition is chronically debilitating and life-threatening, due to long-term neurocognitive and neuroendocrine sequelae, and with poor prognosis of patients with recurrent medulloblastoma.

The condition was estimated to be affecting approximately 0.2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing humanised IgG1 monoclonal antibody against the receptor-binding site of human placental growth factor will be of significant benefit to those affected by the condition. This is based on preclinical data showing improved survival in models of the condition harbouring relapsing/resistant medulloblastoma. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for humanised IgG1 monoclonal antibody against the receptor-binding site of human placental growth factor, for treatment of medulloblastoma, was adopted by consensus.

2.2.22. - EMA/OD/252/16

Treatment of acetaminophen (paracetamol) overdose

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the January 2017 meeting.

2.2.23. - EMA/OD/228/16

Treatment of gastric cancer

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the January 2017 meeting.

2.2.24. Pentosan polysulfate sodium - EMA/OD/130/16

Kyoto Tech Limited; Treatment of interstitial cystitis

COMP coordinator: Annie Lorence/Ingrid Wang

The Committee agreed that the condition, interstitial cystitis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing pentosan polysulfate sodium was considered justified based on preliminary clinical data published in the scientific literature demonstrating that treatment improved symptoms associated with the condition including pain, urinary urgency, and urinary frequency.

The condition is chronically debilitating due to morbidity, which is associated with pain, pressure, or discomfort in the pelvic area as well as increased daytime urinary frequency.

The condition was estimated to be affecting approximately 2 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for pentosan polysulfate sodium, for treatment of interstitial cystitis, was adopted by consensus.

2.2.25. Pr-(D)cysMetPipArgLeuArgSarCys-LysArgProTyrTleLeu-OH - EMA/OD/220/16

VECT-HORUS; Treatment of perinatal asphyxia

COMP coordinator: Giuseppe Capovilla/Dinah Duarte

The Committee agreed that the condition, perinatal asphyxia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing Pr-D-Cys-Met-Pip-Arg-Leu-Arg-Sar-Cys-Lys-Arg-Pro-Tyr-Tle-Leu-OH was considered justified based on preclinical data showing a sustainable and manageable induction of hypothermia in models of the condition.

The condition is chronically debilitating due to the long lasting neurological and developmental sequelae. The condition is also life threatening, with high mortality associated with the most severe cases.

The condition was estimated to be occurring in approximately 1 in 10,000 persons per year in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for Pr-D-Cys-Met-Pip-Arg-Leu-Arg-Sar-Cys-Lys-Arg-Pro-Tyr-Tle-Leu-OH, for treatment of perinatal asphyxia, was adopted by consensus.

2.2.26. Recombinant adeno-associated viral vector serotype 9 containing the human N-α-acetylglucosaminidase gene - EMA/OD/226/16

Ser-mes Planificación SL; Treatment of mucopolysaccharidosis type IIIB (Sanfilippo B syndrome)

COMP coordinator: Irena Bradinova/Dinah Duarte

The Committee agreed that the condition, mucopolysaccharidosis type IIIB (Sanfilippo B syndrome), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing recombinant adeno-associated viral vector serotype 9 containing the human N-alpha-acetylglucosaminidase gene was considered justified based on an vivo model of the condition, in which treatment with the product resulted in improved histology, motor function and survival.

The condition is chronically debilitating due to severe behavioural abnormalities and progressive dementia and life-threatening with death ensuing typically in the end of the second decade of life.

The condition was estimated to be affecting less than 0.1 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for recombinant adeno-associated viral vector serotype 9 containing the human N-alpha-acetylglucosaminidase gene, for treatment of mucopolysaccharidosis type IIIB (Sanfilippo B syndrome), was adopted by consensus.

2.2.27. - EMA/OD/247/16

Treatment of bronchiolitis obliterans syndrome

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to respond in writing before the Committee at the January 2017 meeting.

2.2.28. - EMA/OD/249/16

Treatment of glioma

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the January 2017 meeting.

2.2.29. Recombinant IgG degrading enzyme of *Streptococcus pyogenes* - EMA/OD/237/16

Hansa Medical AB; Prevention of graft rejection following solid organ transplantation

COMP coordinator: Frauke Naumann-Winter

Following review of the application by the Committee, it was agreed to broaden/rename the active substance to recombinant IgG degrading enzyme of *Streptococcus pyogenes.*

The Committee agreed that the condition, graft rejection following solid organ transplantation, is a distinct medical entity and meets the criteria for orphan designation.

The intention to prevent the condition with the medicinal product containing recombinant IgG degrading enzyme of *Streptococcus pyogenes* was considered justified based on preliminary clinical data showing successful kidney transplantation in patients with high levels of donor specific anti-human leukocyte antigen antibodies when the product was administered before transplantation.

The condition is life-threatening and chronically debilitating due to intestinal inflammation causing diarrhoea, abdominal pain, nausea and vomiting, as well as skin and mucosal damage, sicca syndrome, cholestasis, arthritis, obliterative bronchiolitis and the need for immunosuppression that increases susceptibility to infections.

The population of patients eligible for prevention of the condition was estimated to be approximately 0.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of prevention of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant IgG degrading enzyme of *Streptococcus pyogenes* will be of significant benefit to the population at risk of developing the condition. The proposed product targets patients with donor specific anti-HLA antibodies, for whom no satisfactory prevention method exists. The sponsor has provided preliminary clinical data demonstrating successful kidney transplantation in patients with high levels of donor specific anti-human leukocyte antigen antibodies when the product was administered before transplantation. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for recombinant IgG degrading enzyme of *Streptococcus pyogenes*, for prevention of graft rejection following solid organ transplantation, was adopted by consensus.

2.2.30. - EMA/OD/224/16

Treatment of cystic fibrosis

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the January 2017 meeting.

2.2.31. - EMA/OD/245/16

Treatment of ovarian cancer

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the January 2017 meeting.

2.2.32. - EMA/OD/221/16

Treatment of Dravet syndrome

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the January 2017 meeting.

2.2.33. Trans-resveratrol - EMA/OD/209/16

Luis Pereira de Almeida; Treatment of spinocerebellar ataxia

COMP coordinator: Dinah Duarte/Violeta Stoyanova

The Committee agreed that the condition, spinocerebellar ataxia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing trans-resveratrol was considered justified based on preclinical data in a relevant disease model for spinocerebellar ataxia type 3 demonstrating that treatment was able to improve motor function.

The condition is chronically debilitating due to slowly progressive incoordination of gait which is often associated with poor coordination of hands, speech, and eye movements.

The condition was estimated to be affecting approximately 0.2 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for trans-resveratrol, for treatment of spinocerebellar ataxia, was adopted by consensus.

2.3. Amendment of existing orphan designation

2.3.1. Synthetic double-stranded siRNA oligonucleotide directed against transthyretin Mrna – EMA/OD/142/10, EU/3/11/857

Alnylam UK Limited - United Kingdom; Treatment of familial amyloid polyneuropathy

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to respond in writing before the Committee at the January 2017 meeting.

2.3.2. Raxibacumab for treatment of inhalation anthrax disease - EMA/OD/134/14, EU/3/14/1352

The EMA received from the sponsor a request for clarification of the condition/indication. The COMP discussed the request and confirmed that the proposed therapeutic indication was part of the orphan treatment indication. The sponsor was informed of the outcome of the discussion.

2.3.3. Ciclosporin (inhalation use) for the treatment of graft rejection after lung transplantation - EMEA/OD/022/04, EU/3/04/210

The EMA received from the sponsor a request for clarification of the condition/indication. The COMP discussed if the condition should be amended to better reflect the proposed indication or if it would be preferable to apply for a second designation. The COMP

recommended an amendment of the current designation. The sponsor was informed of the outcome of the discussion.

2.4. COMP opinions adopted via written procedure following previous meeting

2.4.1. 20% intravenous fat emulsion consisting of 20% soybean oil, 1.2% egg yolk phospholipids, 2.25% glycerin, and water for injection - EMA/OD/062/16

Alan Boyd Consultants Ltd; Treatment of poisoning by local anaesthetics

COMP coordinator: Violeta Stoyanova

Action: For information

Document tabled:
Summary report

2.5. Appeal

None

2.6. Nominations

2.6.1. New applications for orphan medicinal product designation - Appointment of COMP coordinators

COMP coordinators were appointed for 21 applications submitted.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 22 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

None

3.2. Finalised letters

3.2.1. -

Treatment in haematopoietic stem cell transplantation

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of paroxysmal nocturnal haemoglobinuria

The new request was noted.

3.3.2. -

Treatment of autosomal dominant polycystic kidney disease

The new request was noted.

3.3.3. -

Treatment of glioma

The new request was noted.

4. Review of orphan designation for orphan medicinal products for marketing authorisation

4.1. Orphan designated products for which CHMP opinions have been adopted

4.1.1. Cystadrops (mercaptamine) - EMA/OD/036/08, EU/3/08/578, EMEA/H/C/003769

Orphan Europe S.A.R.L.; Treatment of cystinosis

COMP coordinator: Lesley Greene / Geraldine O'Dea

The COMP concluded that:

The proposed therapeutic indication, treatment of corneal cystine crystal deposits in adults and children from 2 years of age with cystinosis falls entirely within the scope of the orphan indication of the designated orphan medicinal product, treatment of cystinosis.

The prevalence of cystinosis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.1 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating and life-threatening, in particular due to progressive impairment of renal function leading to renal failure and of other organs, and the development of ocular symptoms including loss of visual acuity, photophobia and keratopathy.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Cystadrops will be of significant benefit is supported by clinical data which shows that the product offers a clinically relevant advantage as it treats patients with corneal cystine crystal deposits where currently there are no authorised topical products.

An opinion not recommending the removal of Cystadrops, cysteamine hydrochloride, mercaptamine (EU/3/08/578) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion will be endorsed for publication on the EMA website.

4.2. Orphan designated products for discussion prior to adoption of CHMP opinion

4.2.1. Ledaga - chlormethine –EMA/OD/112/11, EU/3/12/963, EMEA/H/C/002826

Actelion Registration Ltd.; Treatment of cutaneous T-cell lymphoma

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the January 2017 meeting.

Notes:
Status of the procedure at the CHMP: Expected opinion in December 2016

4.3. On-going procedures

COMP co-ordinators were appointed for 5 applications.

4.4. Public Summary of Opinion

None

5. Application of Article 8(2) of the Orphan Regulation

None

6. Organisational, regulatory and methodological matters

6.1. Mandate and organisation of the COMP

6.1.1. Strategic Review & Learning meetings

COMP Strategy Review & Learning meetings, 20-21 March 2016, Valletta, Malta

The COMP discussed the preliminary agenda.

Document tabled:
Draft Agenda

6.1.2. Protocol Assistance Working Group

Cancelled

6.1.3. COMP Drafting Group

Cancelled

6.1.4. Preclinical Models Working Group

The working group on Preclinical Models met on 08 December 2016.

6.1.5. Recommendations on eligibility to PRIME – report from CHMP

Documents were circulated in MMD.

Document(s) tabled:
PRIME eligibility requests - list of adopted outcomes October 2016

6.1.6. Updated policy on handling competing interests for scientific committees' members and experts

The COMP was informed on the updated policy.

Document(s) tabled:
Policy 0044 - European Medicines Agency policy on the handling of competing interests of scientific committees' members and experts

6.1.7. Survey to Committee members, alternates and concerned NCA staff on the service and support provided by EMA Committee Secretariats - Findings

Postponed to January 2017

6.1.8. COMP Membership

The COMP welcomed Fernando Méndez Hermida as new member representing Spain.

6.2. Coordination with EMA Scientific Committees or CMDh-v

6.2.1. PDCO/COMP Working Group

The PDCO/COMP working group took place by teleconference on 07 December 2016.

6.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups

6.3.1. Working Party with Patients' and Consumers' Organisations (PCWP)

None

6.3.2. Working Party with Healthcare Professionals' Organisations (HCPWP)

None

6.4. Cooperation within the EU regulatory network

6.4.1. European Commission

Commission Notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on Orphan Medicinal Products

The COMP was informed on the publication of this document.

6.5. Cooperation with International Regulators

6.5.1. Food and Drug Administration (FDA)

The draft agenda of the monthly teleconference with FDA held on 08 November 2016 is available in MMD for information.

6.5.2. Gaucher disease - A Strategic Collaborative Approach from EMA and FDA

The COMP was informed on this initiative with an invitation for participation.

Document tabled:
Gaucher disease

6.5.3. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

6.5.4. The Therapeutic Goods Administration (TGA), Australia

None

6.5.5. Health Canada (HC)

None

6.6. Contacts of the COMP with external parties and interaction with the Interested Parties to the Committee

None

6.7. COMP work plan

6.7.1. COMP Work Plan 2016

Documents were circulated in MMD.

Document(s) tabled:
COMP Work Plan 2016
COMP Work plan tracking tool 2016

6.7.2. COMP Work Plan 2017

COMP adopted the proposed work plan for 2017 and the list of COMP members volunteered to participate in the different activities.

Document(s) tabled:
COMP draft Work Plan 2017

6.8. Planning and reporting

6.8.1. List of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2016

An updated list of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2016 were circulated.

6.8.2. Overview of orphan marketing authorisations/applications

An updated overview of orphan applications for Marketing Authorisation was circulated.

7. Any other business

7.1. EMA Business Pipeline activity and Horizon scanning

Documents were circulated in MMD.

Document tabled:
2017 forecast of the Business Pipeline report for the human scientific committees

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 06-08 December 2016 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Bruno Sepodes	Chair	Expert recommended by EMA	No interests declared	
Brigitte Blöchl-Daum	Member	Austria	No interests declared	
Irena Bradinova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No restrictions applicable to this meeting	
Katerina Kopeckova	Member	Czech Republic	No restrictions applicable to this meeting	
Jens Ersbøll	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Annie Lorence	Member	France	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Nikolaos Sypsas	Member	Greece	No restrictions applicable to this meeting	
Melinda Sobor	Member	Hungary	No interests declared	
Sigurdur B. Thorsteinsson	Member	Iceland	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member	Italy	No interests declared	
Irena Rogovska	Member	Latvia	No interests declared	
Aušra Matulevičienė	Member	Lithuania	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No interests declared	
Violeta Stoyanova-Beninska	Member	Netherlands	No interests declared	
Ingrid Wang	Member	Norway	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	No interests declared	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovak Republic	No interests declared	
Fernando Mendez Hermida	Member	Spain	No interests declared	
Dan Henrohn	Member	Sweden	No restrictions applicable to this meeting	
Daniel O'Connor	Member	United Kingdom	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Lesley Greene	Member (Vice-Chair)	Patients' Organisation Representative	No interests declared	
Mario Ricciardi	Member	Patients' Organisation Representative	No interests declared	
Kerstin Westermark	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Virginie Hivert	Expert - in person*	Patients' Organisation Representative	No restrictions applicable to this meeting	
Julian Isla	Expert - in person*	Patients' Organisation Representative	No interests declared	2.2.32.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

* Experts were only evaluated against the agenda topics or activities they participated in.

Explanatory notes

The notes below give a brief explanation of the main sections and headings in the COMP agenda and should be read in conjunction with the agenda or the minutes.

Abbreviations / Acronyms

CHMP: Committee for Medicinal Product for Human Use
COMP: Committee for Orphan Medicinal Products
EC: European Commission
FAL: Final Advice Letter
OD: Orphan Designation
OMPD: Orphan Medicinal Product Designation
PA: Protocol Assistance
PDCO: Paediatric Committee
PRAC: Pharmacovigilance and Risk Assessment Committee
SA: Scientific Advice
SAWP: Scientific Advice Working Party

Orphan Designation (*section 2 Applications for orphan medicinal product designation*)

The orphan designation is the appellation given to certain medicinal products under development that are intended to diagnose, prevent or treat rare conditions when they meet a pre-defined set of criteria foreseen in the legislation. Medicinal products which get the orphan status benefit from several incentives (fee reductions for regulatory procedures (including protocol assistance), national incentives for research and development, 10-year market exclusivity) aiming at stimulating the development and availability of treatments for patients suffering from rare diseases.
Orphan Designations are granted by Decisions of the European Commission based on opinions from the COMP. Orphan designated medicinal products are entered in the Community Register of Orphan Medicinal Products.

Protocol Assistance (*section 3 Requests for protocol assistance with significant benefit question*)

The protocol assistance is the help provided by the Agency to the sponsor of an orphan medicinal product, on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product in view of the submission of an application for marketing authorisation.

Sponsor

Any legal or physical person, established in the Community, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product.

Maintenance of Orphan Designation (*section 4 Review of orphan designation for orphan medicinal products for marketing authorisation*).

At the time of marketing authorisation, the COMP will check if all criteria for orphan designation are still met. The designated orphan medicinal product should be removed from the Community Register of Orphan Medicinal Products if it is established that the criteria laid down in the legislation are no longer met.

More detailed information on the above terms can be found on the EMA website: www.ema.europa.eu/